AN ADDRESS ON MALARIAL FEVER

DELIVERED BEFORE THE CLEVELAND MEDICAL SOCIETY

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Reprint from the CLEVELAND JOURNAL OF MEDICINE

June, 1897

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GENTLEMEN: In the few words I wish to say tonight I shall endeavor to bring together some of the more important points which have been added to our knowledge concerning malarial fever since the discovery of the specific parasite sixteen years ago, and to emphasize their practical significance. I am aware that in Cleveland the disease is relatively rare, and yet its occasional occurrence and its interesting relations from a point of view of diagnosis with various other affections which are common with you here, as well as with us farther south, have suggested to me that a brief discussion of the subject might not be without interest.

Let us first consider the pathogenic agent. From time immemorial the prevalence of fevers in damp and marshy districts has been known. In old times, however, the malarial fevers were not sharply differentiated from various other febrile processes; in particular, typhus, typhoid, relapsing fevers and other septic infections. After the introduction of quinine, Torti, in 1712, differentiated a special class of fevers which yielded to treatment by this drug. These fevers, which occur especially in warm and tropical countries, and in damp, marshy regions, showed frequently an intermittent character, and to them the term "malaria" came to be applied.

It is very remarkable how early the infectious nature of malaria was suspected. Varro (B. C. 118-29) says: "*Advertendum etiam si qua erunt loca palustria et propter easdem causas, et quod arescunt, crescunt animalia quaedam minuta, quae non possunt oculi consequi, et per aera intus in corpus per os, ac nares perveniunt atque efficiunt difficiles morbos.*"

Thus, we see that not only was the infectious nature of the process suspected, but further, the infectious agent was believed to be an animal parasite. These views were maintained in 1716 by Lancisi, and later by Rasori and a number of other Italian observers.

The general idea which was held concerning the manner of entrance of the infectious agent into the organism is reflected by the popular term which has since become definitely attached to the disease. The word "malaria" is nothing more than the Italian expression "*mal' aria*"—bad air. But these older ideas concerning the animate nature of the virus of malaria gave way gradually, especially during the early part of this century, to the theory that the parasite was of vegetable origin, this view having been especially put forward by Mitchell and Salisbury in this country.

In 1879 Klebs and Tommasi Crudelli described a bacillus which they believed to be the infectious agent of malaria. This they obtained from the

earth in malarious districts. Their observations, though incomplete and soon disproven, gained considerable credence; so much so that fifteen years after the discovery of the true parasite one of the leading medical journals, published in the English language, referred in an editorial to the opinions of these authors as settled facts.

In 1880 Laveran, a French army surgeon in Algiers, discovered in the blood of patients with malarial fever living organisms, which develop in the red blood-corpuscles of the affected individual, at the expense of which they grow and accumulate dark pigment-granules. These organisms are readily demonstrable microscopically, either in the fresh blood or in dried and stained specimens.

From the universal presence of these parasites in the blood of patients with malarial fever, their immediate disappearance with recovery, either spontaneous or under treatment by quinine, Laveran believed himself justified in assuming that they represented the true pathogenic agent of the malady. Despite the opposition which the discovery of Laveran met with at first, you well know how universal has been its confirmation by all observers who have had opportunity to properly study the disease. The great value of this advance, apart from the light which it has thrown upon the general pathology of malarial fever, is readily appreciated when we consider that it has furnished us with a simple and certain method of diagnosis of the disease.

Now, though the discovery of the presence of a living animal parasite in the blood of all patients with malarial fever—a parasite which disappears with the recovery—is strong presumptive evidence of the intimate relation between the symptoms and the organism; yet we must acknowledge that only one of Koch's three postulates essential to determine the causal relation between the parasite and the disease has been fulfilled. For the absolute proof of this causal relation we need in addition:

(*a*) To obtain the organism in pure culture outside the body;

(*b*) To transfer the disease by inoculation from the pure culture into healthy individuals.

The cultivation of the parasite outside the body has never yet been accomplished, but we have in the blood of the infected individual, which is otherwise sterile, essentially an already prepared pure culture; and repeated experiments by Italian, Russian and German observers have shown that intravenous or hypodermic inoculation of the blood of an infected individual will always transfer the infection.

As has already been said, Laveran's discovery has been almost universally confirmed by all observers who have had opportunity to properly study the disease. And to our credit be it said that our countrymen have been among the foremost in continuing his work—Councilman and Abbott, Sternberg, Osler, James and Dock having early recognized the importance and value of the discovery.

After Laveran, the next great advance was made by Golgi, who, in 1885, studied the parasites observed in quartan and tertian fever, tracing all the steps in their life-history and reproduction, and noting the remarkable relation which exists between the development of the parasites and the clinical manifestations of the fever. Further studies by Roman observers and also by Golgi of the more irregular and pernicious fevers occurring in the tropics, and during the later summer and fall in temperate climates, have led us to recognize today three main types of the fever, each of which is associated with a special type of the malarial parasite:

(1) *Tertian fever.*

(2) *Quartan fever.* These may be classed as the regularly intermittent fevers; they occur in temperate climates throughout the malarial season, forming the only cases in the earlier part of the year.

(3) The more irregular fevers which have been termed by the Italians the "*aestivo-autumnal*" *fever.* This type of the disease occurs commonly in the tropics, but in temperate climates it is observed only during the height of the malarial season; that is, during the later summer and early fall.

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The Parasites of the Regularly Intermittent Fevers; the Tertian and Quartan Parasites.

We now know that in tertian and quartan fever the parasites exist in the blood in enormous groups, all the members of which are approximately at the same stage of development. The parasites constituting such a group enter the red corpuscles as small, clear, amœboid, hyaline bodies, which develop within the corpuscles, increasing in size and accumulating dark pigment-granules as a result of the destruction of the hemoglobin of the containing element. When the parasite is fully developed the pigment gathers into a single block or a clump of coarse granules, and the organism breaks up into a number of small, round hyaline bodies, each of which represents a fresh young parasite. These small hyaline bodies enter fresh red blood-corpuscles and pursue again their cycle of development.

The length of the cycle of development of a group of tertian parasites lasts almost exactly 48 hours; so that, if one group be present in the blood, sporulation will occur every other day. On the other hand, the cycle of existence of the quartan parasite lasts approximately 72 hours, sporulation occurring every fourth day.

Now, the remarkable fact was discovered by Golgi that the malarial paroxysm is always associated with the sporulation of one of these groups of parasites. Thus, if one group of tertian parasites be present in the blood, sporulation will occur every other day, and with every period of sporulation there will occur a typical malarial paroxysm—*tertian intermittent fever.*

In infection with quartan organisms, whose cycle of existence is longer, lasting 72 hours, sporulation and the resulting paroxysm occur only every

fourth day—*quartan intermittent fever*. Furthermore, it has been shown that, all things being equal, the severity of the manifestations of the infection depends largely upon the number of parasites actually present.

The mere existence of parasites in the blood is not sufficient to produce fever; the group must reach by multiplication a certain sufficient size. Thus, ordinarily, a considerable period of incubation is required for the development of malarial fever, during which time a group of parasites is passing through its regular cycle and reaching over larger proportions by its gradual multiplication. In experimental infections it requires usually about ten days or two weeks for the parasites inoculated to reach by multiplication a number sufficient to produce well marked manifestations.

Not infrequently more than one group of the tertian or quartan organisms may be present, but more than two groups of the tertian or three of the quartan are extremely rare. In infections with two groups of the tertian organisms the parasites reach maturity, almost invaribly, upon successive days; the result thus is *quotidian intermittent fever*. When two or three groups of the quartan organism are present, they also arrive at maturity usually on successive days, so that there follow either two days with intermittent paroxysms, followed by one day of complete intermission, or a quotidian fever due to three groups of the parasite.

The morphological differences between the tertian and quartan parasites it is impossible to enter into at length in so short a space as is allotted to me tonight. You will observe upon the chart the main points of difference, which are well marked. The most important are the greater size of the tertian organism, its greater amœboid activity, the larger number, greater activity and smaller size of the pigment-granules; the fact that it breaks up into a larger number of spores than does the quartan organism, while the containing red corpuscle becomes gradually expanded and decolorized. The quartan parasite as you see is smaller; the granules are less motile, less numerous and coarser; the parasite breaks into a smaller number of segments, while the containing red corpuscle becomes rather contracted and deeper colored.

The Aestivo-autumnal Parasite. The third variety of fever, the æstivo-autumnal fever, is associated with the presence of organisms which possess distinct morphological and biological differences from those described above, the chief being their much smaller size. There are, however, certain other important biological variations. They develop, for instance, largely in the internal organs, appearing in the peripheral circulation only during the earliest stages of their existence, when they are represented by small amœboid, non-pigmented, hyaline bodies. The larger forms, forms containing more than a few scattered granules of pigment, are relatively rare in the peripheral circulation; the segmenting bodies are only found in the blood of certain internal organs, especially the spleen, bone-marrow, brain and liver. I have

seen segmenting bodies in the peripheral circulation but three times in this type of fever.

In this type of malaria there appear, also, after the infection has lasted about a week, larger pigmented crescentic or ovoid bodies, which do not apparently pursue the ordinary cycle of development, bodies which are very resistant to quinine. They represent probably sterile forms as long as they remain in the blood, though it cannot be denied that, as some maintain, they may be capable of further development outside the body.

A striking biological feature of the æstivo-autumnal parasite, or, as Dr. Welch has happily termed it, "*Haematozoon falciparum*," is the fact that the organisms are often accumulated in great numbers in certain special parts of the body. These special localizations of the parasite in various internal organs may give rise by the changes there produced to distinct clinical symptoms.

Another difference from the organisms of the regularly intermittent fevers is the fact that they are often present in multiple groups or sometimes in great numbers, apparently at almost all stages of development, so that the regular arrangement in groups is lost. In those cases in which distinct groups may be made out the length of the cycle of existence appears to vary from 24 to 48 hours, or a little more.

Marchiafava and Bignami believe that they can distinguish morphologically and biologically two varieties of these parasites, one with a shorter and the other with a longer cycle, a view, however, which we have been unable to confirm.

The fevers with which these organisms are associated show, as one might expect, a much more irregular course than do the tertian and quartan fevers, and, not infrequently, there may be an irregularly remittent elevation of temperature.

In summary, then, we may say that we must now recognize:

(*a*) That malarial fever is due to infection with hemocytozoa, which develop within the red corpuscle;

(*b*) That three varieties or more probably species of these organisms are to be distinguished, each associated with a distinct type of fever—namely, the tertian, the quartan, and the æstivo-autumnal parasites.

(*c*) That these parasites, in the regularly intermittent fevers, are present in great groups, all the members of which are approximately at the same stage of development.

(*d*) That the same is often true of the æstivo-autumnal parasite, though the tendency toward multiplication and the obliteration of sharply distinguishable groups is much more marked.

(*e*) That the malarial paroxysm occurs always in association with the sporulation of a group of parasites.

(*f*) That the severity of the symptoms in any given infection depends to a great extent upon the number of parasites present.

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We have seen that the causal relation of the parasites to malarial infections may be regarded as a settled fact. Let us now consider more intimately the manner in which the parasites bring about the clinical manifestations.

The Febrile Paroxysm.—The observations of Golgi which have been almost universally confirmed, show that the malarial paroxysm is always coincident with the sporulation of a group of parasites. The intermittent fever is thus easily accounted for by the remarkable arrangement of the parasites in groups sporulating at regular intervals, as has been already referred to. In infections with the æstivo-autumnal parasites, in which the groups are so frequently multiple, or in which, indeed, this arrangement may be absent, the fever, as one might expect, is often irregular or continuous.

But why should the sporulation of a group of parasites be followed by fever?

Golgi first suggested that the fever was the result of the invasion of the red corpuscles by the fresh young spores arising at the time of segmentation.

But Antolisei, by a simple clinical observation, which may be confirmed at any time by the bedside, showed that this could not be the case. He called attention to the fact that if a large dose of quinine be given just before a malarial paroxysm, the segmentation of the ripe group of parasites will not be hindered, but the new organisms will all be destroyed before they enter fresh red blood-corpuscles; no fresh invasion of red elements takes place and the parasites disappear from the blood. The impending paroxysm occurs just the same, but no further symptoms follow. It cannot then be the invasion of fresh red corpuscles by the young parasites which is responsible for the paroxysm, but rather something which occurs at the time of sporulation.

Baccelli was the first to suggest, from analogy with other infectious processes, that the paroxysm is due to a circulating toxic substance set free by the parasites at the time of sporulation. This view, which seems most rational, has been accepted by most observers, and, indeed, there is much to support it.

That the chill and fever are produced by toxic substances in the circulation is strongly suggested for the following reasons:

1. Analogy with other infectious processes.

2. The fact that observations by Brousse, Roque and Lemoine, Botazzo and Pensuti have shown that there is a marked increase in the toxicity of the urine passed during and just following the malarial paroxysm.

3. The greatly increased toxicity of the sweat obtained during the malarial paroxysm as compared with that of normal individuals, as shown by the observations of Queirolo.

4. The strongest evidence, however, of the existence of a circulating toxic substance is found in the presence in the organs of patients dead of acute malarial infection of areas of disseminated focal necrosis, closely similar to those which occur in various other severe infectious diseases. These areas have been clearly shown by Flexner to be pathognomonic of a general toxemia.

We have thus practically conclusive evidence of the existence of some toxic substance circulating in the blood. Is this a specific toxine set free by the hematozoa, or may it, perhaps, be the result of changes produced in the organs or tissues by the action of the parasites, such as, perhaps, the destruction of numerous red corpuscles, with the setting free of a considerable quantity of hemoglobin?

Let us consider what happens at the time of the paroxysm. The paroxysm, as has been said, immediately follows and is intimately associated with the sporulation of a group of malarial parasites. There occurs at this period:

1. The segmentation of a large number of full-grown parasites into fresh young organisms, while the pigment (and possibly some small quantity of the cytoplasm of the parasites) are left behind.

2. The liberation of a large number of full-grown and segmenting organisms, while the including red corpuscles are disintegrated and destroyed, and the remains of these, together with a certain amount of hemoglobin which they yet contain, are left to be cared for in the circulation.

3. The escape from the red corpuscles of a considerable number of full-grown parasites which become degenerated and fragmented. These, with the remnants of the segmenting forms are usually engulfed by phagocytes.

4. The rupture of a certain number of uninfected red corpuscles which set free their hemoglobin in the general circulation.

We might imagine that these toxic substances arising at the time of the paroxysm result from the destruction and disintegration of a large number of red blood-corpuscles; or that they are liberated by the parasites themselves at the time of sporulation, and possibly also by the fragmenting full-grown forms which are usually to be seen at this period; or we may imagine that both these factors play a part.

It may be that the destruction of a large number of red corpuscles exerts a toxic influence upon the organism. In other conditions, however, in which this occurs, it is difficult to separate the effect of the blood-destruction from that of the exciting cause, while extensive blood-destruction is by no means always associated with a sharp febrile paroxysm. Thus, in poisoning by chlorate of potassium or carbon monoxide, when great numbers of red blood-corpuscles are destroyed, with consequent hemoglobinuria, fever may be practically absent.

There are, then, many reasons which might induce us to believe that Baccelli's supposition is true; that the toxic substance or substances responsible for the paroxysm are liberated by the sporulating parasites. The remains of the disintegrated red corpuscles may exert a toxic effect, but it is scarcely probable that they play the primary part in exciting the paroxysm.

The Anaemia.—The discovery of the malarial parasite has enabled us easily to account for the anæmia which is so characteristic of malarial infections. This depends not only upon the constant destruction of the red blood-corpuscles in the circulating blood, but in more chronic cases upon the extensive changes in the blood-forming organs which are brought about by the infection.

The jaundice also is a direct result of the extensive blood-destruction. It is not, strictly speaking, hematogenous. The remains of the destroyed red blood-corpuscles and the hemoglobin set free are disposed of ordinarily by the liver through the bile; the increased blood-destruction results in so extensive a polycholia that from the inspissation of the bile and the overcrowding of the bile capillaries, absorption of bile with jaundice occurs.

Pernicious Symptoms.—But among the most interesting results which have followed the recent studies of malarial infections have been the explanations which we have found for some of the pernicious symptoms which are especially common in æstivo-autumnal infections. These symptoms have been shown to be in many instances directly due to the special localization of the parasites in certain internal organs.

Cerebral Symptoms.—The frequency of cerebral symptoms in pernicious malaria is well known. Often, probably, the delirium and other manifestations are due to circulating poisons, but in many cases with symptoms referable to disturbed brain functions, coma, general or local convulsions or paralyses, post-mortem examinations have clearly demonstrated their dependence upon local disturbances produced by the accumulation and development of enormous numbers of parasites in certain parts of the central nervous system. In many cases of fatal comatose malaria the capillaries of the grey cortex throughout may be crowded with parasites free and in red corpuscles. In some instances actual thromboses may occur, resulting in serious local changes. Sometimes definite local symptoms have been shown post-mortem to be due to changes resulting from the special accumulation of parasites in small areas of the brain or cord. Thus, in one instance of pernicious fever, with symptoms of bulbar paralysis, Marchiafava was able to demonstrate post-mortem a special localization of the parasites, with quite extensive secondary changes in the *medulla oblongata*. In like manner the well-known choleriform type of pernicious paroxysm has been shown to be due to the special localization of enormous numbers of parasites in the gastro-intestinal mucosa.

It may be that those instances of pernicious fever, which I have never had the opportunity to observe, but which have been well described by Baccelli in particular, those cases associated with marked pulmonary symptoms, are due to a special localization of the parasites in the capillaries of the lungs.

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Manner of Infection.—From what I have said it is easy to appreciate how deep an insight we have gained into the causes and nature of this important disease, and yet much remains to be done. For instance, we have no idea as to the form in which the malarial parasite exists outside the human body, nor of the manner in which infection occurs. Owing to our ignorance of the former condition we are naturally more or less at sea in our attempts to elucidate the manner of infection. Does infection occur through the respired air, or through the gastro-intestinal tract? Or may it possibly be transmitted subcutaneously by means, perhaps, of insect bites?

You well know how general the idea is that malarial infection takes place by means of the inspired air. Indeed, there seems to be almost overwhelming evidence in favor of the view that infection may take place in this manner. And yet definite proof we do not possess.

In like manner many observers believe that malaria may be a water-borne disease. It must, however, be said that numerous attempts by Celli, Marino and Zeri to produce infection by the administration of water from the most malarious districts, by the mouth, by rectum and as an inhalation, have failed. Grassi and Feletti have furthermore caused patients to drink dew collected from malarial districts, and, indeed, fresh human blood containing malarial parasites, and in every instance with a wholly negative result.

That malaria may be transmitted by hypodermic or intravenous inoculation has been indisputably proved by a large number of carefully carried out experiments. And recently a considerable impetus has been given to the idea that malarial infection may be brought about by the bites of certain insects, especially the mosquito.

Laveran, Bignami and others have called attention to the fact that many of the precautions adopted in severely malarious districts against infection are just such as might be directed against the bites of insects, and especially mosquitoes. The discovery of Theobald Smith that the hemocytozoon (*pyrosoma bigeminum*) of Texas cattle fever is conveyed from one animal to another by means of the cattle-tick, and that of Bruce, that the cause of the tsetse-fly disease is an hemocytozoon which is introduced by bite of the insect, are certainly suggestive, relating, as they do, to parasites so closely allied to the malarial organism.

The theory recently put forward by Manson, who suggests that the mosquito may represent an intermediate host of the malarial parasite,

playing the same rôle that it does in the case *filaria sanguinis hominis,* is very interesting but purely hypothetical. Much of this idea Manson bases upon the discovery that flagellate bodies may develop from crescentic forms within the stomach of the mosquito; but this fact, though very interesting, is not remarkable, when we consider that they develop outside of the body upon the fresh slides of blood. That malarial infection may take place through the bites of insects is an interesting possibility, but it is by no means proven.

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Now, what practical results have we gained from these interesting advances of the last fifteen years? The most important certainly is the establishment of a positive diagnostic criterion; but further, as a direct result of this we have learned much that is important with regard to the methods and effects of treatment.

The only positive diagnostic sign of malarial fever is the discovery of the parasites in the circulating blood. The search for the organism is a relatively simple matter to anyone who is familiar with the use of the microscope and the examination of the blood. It is, however, just as impossible for one who is not familiar with appearances of fresh blood, as well as of its more important pathological changes, to determine the presence or absence of certain forms of the malarial parasite, as it is for one who is ignorant of the kidney to determine fine structural changes in a microscopical section of that organ.

This is a point which should not be forgotten. The study of the blood has until very recently been neglected in our medical institutions, and there are but few who have not paid especial attention to this subject who are capable, without a certain amount of practice and study, of forming an entirely reliable opinion concerning certain forms of the malarial parasite in a specimen of blood. For one who has not paid particular attention to the appearance of fresh or stained specimens of blood, not days, but weeks, nay, even months of study may be necessary before he becomes capable of positively deciding upon the nature of various changes which are not infrequently met with in the circulating blood, changes which sometimes very closely simulate malarial parasites.

On the other hand, it should be said that the large tertian and quartan organisms and the crescentic and ovoid forms occurring in æstivo-autumnal fever are readily recognizable by anyone who has seen them a few times. The positive diagnosis of such cases is easy. In the case, however, of certain of the smaller forms, especially of the æstivo-autumnal parasite, the opinion of a skilled observer alone is reliable, a statement which is, unfortunately, daily proved in current medical literature.

Many physicians who are in active general practice are as unable to give proper time for such examinations as they are to satisfactorily examine

the sputa in many doubtful cases of tuberculosis, but it is always possible for such a physician to prepare dried smears of blood and to send them to an individual who is capable of properly studying them.

Far be it from me to say that the examination of the blood is always necessary for a practical diagnosis of malarial fever. In the vast majority of instances the therapeutic test is sufficient, and one of the greatest benefits which the discovery of the parasite has brought to us has been the definite proof of this fact. This is one of the most important services which the discovery of the parasite has rendered to us. How often previously in fevers which have not presented all the ordinary clinical manifestations of typhoid has the physician remained in doubt as to their possible malarial nature, even after they have failed to yield to quinine!

The discovery of the parasite has taught us that the failure of such a fever to respond within three or four days to the drug is absolute proof of its non-malarial nature. The importance of this fact cannot be overestimated, and no one feels it more than the physician who has practiced for any length of time in a district where both malaria and typhoid fever are common. There is no excuse today for cinchonizing a patient with typhoid fever; if treatment by sufficient doses of quinine prove ineffectual after four days we may abandon our diagnosis of malarial fever.

Another point which the discovery of the parasite has assisted in elucidating is the subject of the so-called "typho-malarial" fevers. Improved methods of observation have shown that the complication of typhoid and malarial fevers is relatively rare. It would indeed be extraordinary if occasional cases did not occur, and such cases are observed, but in these instances the case presents features of a simple complication of two distinct and separate diseases. There is nothing characteristic in the course of such infections. The malaria is as readily amenable to treatment as under other conditions.

The great majority of chills occurring in typhoid fever have nothing whatever to do with malaria; the parasites are not present in the blood and the manifestations are unaffected by quinine. Such chills represent in most instances, probably, secondary infections or auto-intoxications of intestinal origin. There is no such disease as "typho-malarial" fever, and the sooner we cast aside the term the better.

Certain forms of æstivo-autumnal continued malarial fever may, however closely simulate typhoid, and it may not be out of place here to enter for a moment more minutely into the points in differential diagnosis. I have upon the chart a table, taken from a publication now in press* which presents in parallel columns the more important points of difference between the remittent æstivo-autumnal fever and typhoid fever.

REMITTENT FEVER	TYPHOID FEVER
Onset generally intermittent.	Onset gradual and progressive.
Irregular remissions.	Regular, though very slight morning remissions with evening exacerbations of temperature.
The temperature may arrive at 40° (104°) within twenty-four hours.	The temperature does not reach 40° (104°) before the third or fourth day.
Headache rare in the beginning; of a neuralgic character, pulsating, variable in its position and intensity. Sclera subicteric from the onset.	Headache from the beginning; permanent, severe, frontal. Sclera white.
The apathetic expression of the face, the dryness of the tongue, sordes upon the teeth are not very marked.	These symptoms are well marked and progressive.
Breath foul.	Breath has a peculiar mouse-like odor.
The delirium may come on in the early days; it is recurrent but changes with the exacerbations of temperature and other symptoms, and may give way to grave symptoms related to other organs.	Delirium appears only when the disease is well pronounced; it is often persistent and variable only in degree.
If there be pulmonary congestion the cough and other symptoms come on suddenly; the areas affected change from one to the other lobe or lung and may disappear and reappear again with varying intensity; dyspnea is very pronounced; circulatory disturbances are marked, even syncope.	Pulmonary congestion is gradual and persistent; always hypostatic (the bases and dorsal surfaces of the lungs); the dyspnea is less pronounced, and later in appearing, depending more upon the abdominal conditions (tympanites, &c).
There is usually restlessness and anxiety, (jactatatio corporis).	There is usually relaxation, prostration, stupor.
Peculiar greyish yellow color of skin; sometimes a slight jaundice.	No jaundice.
Herpes common.	Herpes rare.
Anæmia more or less marked early in the course.	Anæmia absent excepting in later stages.
No characteristic exanthem; urticaria not uncommon.	Characteristic roseola.
At times there may be transient tympanites or ileo-cecal gurgling; they are but slightly pronounced and paroxysmal; diarrhœa is slight or absent and has not the characters of that in typhoid fever.	Tympanites, gurgling, diarrhœa appear slowly and may become well marked.
No distinct course.	Has a fairly characteristic course.
Urine, high-colored; may show a trace of bile; Ehrlich's diazo reaction rarely present.	Urine high-colored; bile absent; diazo-reaction present during the height of the process.
Blood shows no leucocytosis; eosinophiles not notably diminished; serum does not cause agglomeration of typhoid bacilli (Pfeiffer, Durham and Widal); malarial parasites and pigmented leucocytes present.	Blood shows no leucocytosis; eosinophiles diminished or absent; serum causes agglomeration of typhoid bacilli; malarial parasites and pigment absent.
Fever disappears under quinine.	Fever uninfluenced by quinine.
Is an endemic disease occuring particularly in rural districts; rarely epidemic.	Usually epidemic; prevailing commonly in cities.

*Lectures on the Malarial Fevers. 8vo. D. Appleton & Co.

I doubt if the medical public realizes altogether how much the discovery of the parasite has taught us with relation to this one point in the differential diagnosis of malarial fever. We are carried slowly onward on the river of medical progress into new ideas and theories, and gliding almost unconsciously out of the old forests of obscurity into the ever-widening clearings opened by science, we often forget how much we have learned in a relatively short period of time.

We know today that in Baltimore, for instance, a district where malarial fever is extremely common, fatal malaria is a rare occurrence; we know that, barring a few imported pernicious cases, fatal malarial fever is almost unknown in such a city as New York or Brooklyn, and yet, gentlemen, let me call your attention to a few statistics taken from the United States census for the six years ending in 1890, statistics to which attention has already been called by Dr. Osler. In the city of New York during these six years there were reported:

Deaths from malarial fever, 2,060, or 24.26 per 100,000 of average population.
Deaths from typhoid fever, 2,031, or 24.27 per 100,000 of average population.

In Brooklyn for the same period there were reported:

Deaths from malarial fever, 1,413, or 32.62 per 100,000 of average population.
Deaths from typhoid fever, 1,002, or 23.13 per 100,000 of average population.

In the city of Baltimore during the same period of time there were reported:

Deaths from malarial fever, 934, or 41.51 per 100,000 of average population.
Deaths from typhoid fever, 904, or 40.17 per 100,000 of average population.

Now, gentlemen, during the seven years since the Johns Hopkins Hospital was opened, two of the years being included among those in which these census statistics were compiled, there occurred in the hospital: Deaths from malarial fever, 3; deaths from typhoid fever, 48; a proportion of one death from malarial fever to sixteen from typhoid.

It is wholly safe to say that at least nine-tenths of these reported statistics are incorrect, the vast majority of the so-called cases of malarial fever being doubtless typhoid. And we forget that as short a time as seven years ago we regarded such statistics as these with complacency.

But if the Baltimore statistics are surprising, in Brooklyn and New York, where it is extremely doubtful whether a single case of pernicious malarial fever occurs, apart, perhaps, from a few coming from the tropics, the statistics are simply appalling; and let me repeat, there is no excuse for such statistics today, for the discovery of the parasite has not only given us in itself a sure method of diagnosis, but it has taught us to realize with what complete confidence we may rely upon the therapeutic test with quinin in the differential diagnosis of malarial fever.

The discovery of the malarial parasite has been of invaluable assistance in the differential diagnosis of a number of other manifestations of malaria

which might otherwise be overlooked. This is especially true in certain pernicious paroxysms, particularly the comatose form which is frequently confounded with sunstroke. In algid and choleriform paroxysms, which may occur indeed without a chill and with sub-normal temperature, the examination of the blood may often save life by giving us an immediate diagnosis. The examination of the blood is also of considerable assistance at times in helping us to make a ready diagnosis between early tuberculosis and certain septic conditions associated with intermittent fever. Had we in private practice a carefully-kept two-hourly chart to show us the exact hour of onset and the exact duration of paroxysms in all these instances, our diagnosis might be relatively simple, but we know too well that this is not the case, and confusion between early tuberculosis and malaria in the neighborhood, for instance, of Baltimore is excessively common.

A ready means of differential diagnosis between malarial fever and various post-partum and post-operative infections is afforded us by the presence of the parasite in the blood. Careful observation tends to show that the majority of post-partum and post-operative chills are not malarial in nature, and the early recognition of this fact, as permitted by blood examination, should put us on the lookout for some other septic complication.

Now, gentlemen, can we say with assurance that the malarial parasite is always to be demonstrated in the circulating blood in every malarial infection? May we positively deny the existence of a malarial infection from the absence of the parasite in specimens of the circulating blood? Literally speaking, we cannot, for there are instances of malarial infection in which careful search of the blood fails to show the parasite. Practically, however, we can, for such cases are rare and unimportant. In any case of tertian or quartan fever of sufficient severity to produce symptoms, reasonably careful examination of the blood will always show the malarial parasite. Occasionally, in æstivo-autumnal fever, in which, as has been before noted, the parasites tend often to gather especially in the internal organs, particularly at a period during or just before a paroxysm, the number of parasites in the peripheral circulation may be extremely small, and rarely, though occasionally, a single careful examination may prove negative. Almost invariably, however, a subsequent examination will reveal the parasite.

There are no cases of pernicious malaria in which the parasites are not present in the blood in sufficient quantities to immediately call our attention to the nature of the case.

What have we learned with regard to the treatment of the disease? Much. We have learned, in the first place, that quinine is a true specific. We have definite proof that those occasional cases in which quinine has appeared to be inefficacious are clearly not cases of malaria, or at least are cases in which there is a complicating disease.

We have been confirmed in our ideas as to the time when quinine should be given to the most efficacious, by the explanation of the cause of its action. It has been shown that the organisms are most readily affected at the time when they are free in the circulation, and that period only occurs at the time of sporulation, namely, just before and during the paroxysm.

In ordinary intermittent fevers a sufficient dose of quinine, given just at the time of the paroxysm, will almost entirely destroy the group of parasites then segmenting, and will prevent, for some time, at least, further manifestations on the part of that group of parasites. Continued treatment, however, is usually necessary to entirely destroy the infection. We have then a practical foundation for the fact already made out that the time at which the best result is to be obtained from the administration of large doses of quinine is just at the period of the paroxysm, or at the time when the paroxysm would have occurred, had previous treatment been omitted.

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But I have already passed beyond my proper limit of time. Let me remind you, however, in conclusion, that Laveran's discovery of the parasite, which has done so much to bring order out of the chaos of our continued fevers, was not made by chance; it was the result of carefully planned investigation. Such results as this do more to prove the value of careful, scientific clinical and laboratory observation than books of argument.

We now know the pathogenic agent of malarial fever; we possess a simple and certain method of diagnosis; we have in quinine a true specific remedy for the disease. But we have yet a higher goal to reach. We must discover a means of prevention, and the first step toward this is to discover the method of infection.

It may well be that we are not far from this discovery. It is one of the most hopeful fields for research which is now open to us, and it is a field in which our climate offers us unusual opportunities for study.

Let us hope that we in America may play as honorable a rôle in the clearing up of the obscure questions connected with malaria as did our illustrious predecessors, the little group of students of Louis, in the differentiation of typhus and typhoid fever.